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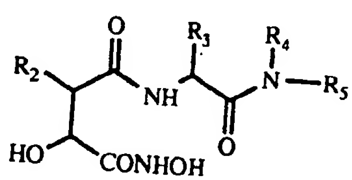
(54) Title: HYDROXAMIC ACID DERIVATIVES AS METALLOPROTEINASE INHIBITORS



(I)

(57) Abstract

Compounds of formula (I) have matrix metalloproteinase inhibitory activity, wherein R_2 represents a group R_6-A- wherein A represents a divalent straight or branched, saturated or unsaturated hydrocarbon chain of up to 6 C atoms which may be interrupted by an O or S atom, and R_6 represents hydrogen or an optionally substituted phenyl, cycloalkyl or cycloalkenyl group; R_3 represents a group R_7-$(B)_n$- wherein n is 0 or 1, B represents a divalent straight or branched, saturated or unsaturated hydrocarbon chain of up to 6 C atoms which may be interrupted by an O or S atom, and R_7 is -CONHOH, carboxyl, esterified or amidated carboxyl, cycloalkyl, cycloalkenyl, heterocyclyl, phenyl, naphtyl, or substituted phenyl or naphtyl in which the substituent(s) are selected from phenyl, hydroxy, C_1-C_6 alkoxy, benzyloxy, or R_8-(C=O)-(C_1-C_6alkyl)-O- wherein R_8 is hydroxy, amino, or an amino acid residue linked via an amide bond; or (except when n=0) R_7 is hydrogen; R_4 represents hydrogen or methyl; R_5 represents hydrogen, C_1-C_6 alkyl or a group D-(C_1-C_6 alkyl) wherein D represents hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, acylamino, optionally substituted phenyl, or a heterocyclic group, NH_2, or a mono- or di-(C_1-NC_6 alkyl) amine or a heterocyclic group; or R_3 and R_5 taken together represent a divalent, saturated or unsaturated hydrocarbon chain of from 8-14 C atoms, which may be interrupted by an O, S or N heteroatom, or a salt, solvate or hydrate thereof, *provided that* R_3 is not the characteristic side chain of a natural alpha-amino acid, or the characteristic side chain of a natural alpha-amino acid in which any functional substituents are protected, any amino groups are acylated, and any carboxyl groups are esterified.

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Hydroxamic Acid Derivatives as Metalloproteinase Inhibitors

The present invention relates to therapeutically active hydroxamic acid derivatives, to processes for their preparation, to pharmaceutical compositions containing them, and to the use of such compounds in medicine. In particular, the compounds are inhibitors of metalloproteinases involved in tissue degradation, and in addition are inhibitors of the release of tumour necrosis factor from cells.

Compounds which have the property of inhibiting the action of metalloproteinases involved in connective tissue breakdown such as collagenase, stromelysin and gelatinase (known as "matrix metalloproteinases", and herein referred to as MMPs) are thought to be potentially useful for the treatment or prophylaxis of conditions involving such tissue breakdown, for example rheumatoid arthritis, osteoarthritis, osteopenias such as osteoporosis, periodontitis, gingivitis, corneal epidermal or gastric ulceration, and tumour metastasis, invasion and growth.

Tumour necrosis factor (herein referred to as "TNF") is a cytokine which is produced initially as a cell-associated 28kD precursor. It is released as an active, 17kD form , which can mediate a large number of deleterious effects *in vivo*. When administered to animals or humans it causes inflammation, fever, cardiovascular effects, haemorrhage, coagulation and acute phase responses, similar to those seen during acute infections and shock states. Chronic administration can also cause cachexia and anorexia. Accumulation of excessive TNF can be lethal.

There is considerable evidence from animal model studies that blocking the effects of TNF with specific antibodies can be beneficial in acute infections, shock states, graft versus host reactions and autoimmune disease. TNF is also an autocrine growth factor for some myelomas and lymphomas and can act to inhibit normal haematopoiesis in patients with these tumours.

Compounds which inhibit the production or action of TNF are therefore thought to be potentially useful for the treatment or prophylaxis of many inflammatory, infectious, immunological or malignant diseases. These include, but are not restricted to, septic shock, haemodynamic shock and sepsis syndrome, post

ischaemic reperfusion injury, malaria, Crohn's disease, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, autoimmune disease, rheumatoid arthritis, multiple sclerosis, radiation damage, toxicity following administration of immunosuppressive monoclonal antibodies such as OKT3 or CAMPATH-1 and hyperoxic alveolar injury.

Since excessive TNF production has been noted in several diseases or conditions also characterised by MMP-mediated tissue degradation, compounds which inhibit both MMPs and TNF production may have particular advantages in the treatment or prophylaxis of diseases or conditions in which both mechanisms are involved.

Several classes of MMP inhibitors have been proposed, including derivatives of hydroxamic acid. The following patent publications disclose hydroxamic acid-based MMP inhibitors:

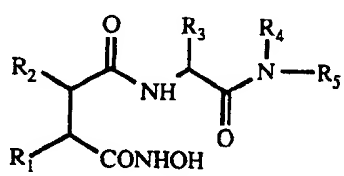
US 4599361	(Searle)
EP-A-0236872	(Roche)
EP-A-0274453	(Bellon)
WO 90/05716	(British Bio-technology)
WO 90/05719	(British Bio-technology)
WO 91/02716	(British Bio-technology)
EP-A-0489577	(Celltech)
EP-A-0489579	(Celltech)
EP-A-0497192	(Roche)
WO 92/13831	(British Bio-technology)
WO 92/22523	(Research Corporation Technologies)
WO 93/09090	(Yamanouchi)

The intrinsic potency of compounds within the broad structural groups of hydroxamic derivatives disclosed in the above publications against particular MMPs can be high. For example, many have a collagenase IC_{50} by the *in vitro* test method of Cawston and Barrett, (Anal. Biochem., **99**, 340-345, 1979) of less than 50 nM. Unfortunately, however, the physicochemical and/or pharmacokinetic

properties of the specific compounds disclosed in those publications have generally been disappointing. Identifying hydroxamic acid-based MMP inhibitors having a good balance of high intrinsic activity against the target MMPs, and good physicochemical and/or pharmacokinetic properties, such that the compounds are easily formulated for administration, have good bioavailability for acceptable periods following administration, and have high *in vivo* activity in the target disease or condition, remains a much sought after goal in the art.

The above patent publications disclose nothing concerning the inhibition of TNF release. Indeed it appears that the state of the art as a whole does not include the recognition of anti-TNF properties in any MMP-inhibiting hydroxamic acid derivatives.

The hydroxamic acid derivatives disclosed in the above publications can be regarded as having the following basic structure (IA):



(IA)

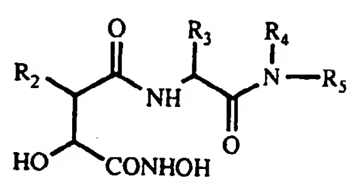
wherein the five substituents R_1 - R_5 may vary according to the detailed disclosure of each publication. The balance of intrinsic level of activity, degree of specificity of inhibition of particular categories of MMP, physicochemical and pharmacokinetic properties can vary in an unpredictable way as the substituents R_1 - R_5 are varied.

Of the above publications, only EP-A-0236872 refers to the possibility that in a particular class of collagenase inhibitors of basic structure (IA) the substituent R_1 may be OH. That possibility is referred to amongst many other possible R_1 substituents, in the context of compounds in which the substituent R_3 is the characteristic side chain of a naturally occurring amino acid in which any functional substituents may be protected, any amino group may be acylated, and any carboxyl group may be esterified. EP-A-0236872 does not disclose such compounds as having preferred or particularly advantageous collagenase

inhibitory properties, and in fact contains no disclosure of any specific compound in which R_1 is hydroxy. It does not address the problem in the art referred to above of providing hydroxamic acid derived MMP inhibitors having the elusive balance of good intrinsic activity profile and good physicochemical and pharmacokinetic properties.

This invention makes available a novel group of compounds of general formula (IA), principally characterised in that the R_1 substituent is a hydroxy group and in which the selected substituent R_3 is not the side chain of a natural amino acid. It has been found that such compounds have in general the sought after but unpredictable combination of desirable formulation characteristics, including good water-solubility, as well as desirable activity profiles as inhibitors of MMP's, including both collagenase and stromelysin inhibitory activity. The class includes compounds which achieve high serum levels following oral administration, and which are active *in vivo* following oral administration in relevant animal models of diseases and conditions mediated by MMP's. Furthermore, as mentioned above, compounds of the invention have been found to have the unexpected and desirable property of inhibiting TNF production.

According to one aspect of the present invention, there is provided a compound of formula (I):



(I)

wherein

R_2 represents a group R_6-A- wherein A represents a divalent straight or branched, saturated or unsaturated hydrocarbon chain of up to 6 C atoms which may be interrupted by an O or S atom, and R_6 represents hydrogen or an optionally substituted phenyl, cycloalkyl or cycloalkenyl group;

R_3 represents a group R_7-$(B)_n$- wherein n is 0 or 1, B represents a divalent

straight or branched, saturated or unsaturated hydrocarbon chain of up to 6 C atoms which may be interrupted by an O or S atom, and R_7 is -CONHOH, carboxyl, esterified or amidated carboxyl, cycloalkyl, cycloalkenyl, heterocyclyl, phenyl, napthyl, or substituted phenyl or napthyl in which the substituent(s) are selected from phenyl, hydroxy, C_1-C_6 alkoxy, benzyloxy, or R_8-(C=O)-(C_1-C_6alkyl)-O- wherein R_8 is hydroxy, amino, or an amino acid residue linked via an amide bond; or (except when n=0) R_7 is hydrogen;

R_4 represents hydrogen or methyl;

R_5 represents hydrogen, C_1-C_6 alkyl or a group D-(C_1-C_6 alkyl) wherein D represents hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, acylamino, optionally substituted phenyl, or a heterocyclic group, NH_2, or a mono- or di-(C_1-C_6 alkyl) amine or a heterocyclic group;

or R_3 and R_5 taken together represent a divalent, saturated or unsaturated hydrocarbon chain of from 8 to 16 C atoms, which may be interrupted by an O, S or N heteroatom,

or a salt, solvate or hydrate thereof,

provided that R_3 is not the characteristic side chain of a natural alpha-amino acid, or the characteristic side chain of a natural alpha-amino acid in which any functional substituents are protected, any amino groups are acylated, and any carboxyl groups are esterified.

As used herein the term "C_1-C_6 alkyl" or "saturated hydrocarbon chain of up to 6 C atoms" refers to a straight or branched chain alkyl moiety having from 1 to 6 carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl and hexyl.

The term "C_2-C_6 alkenyl" or "unsaturated hydrocarbon chain of up to 6 C atoms" refers to a straight or branched chain alkenyl moiety having from 2 to 6 carbon

atoms and having in addition one double bond of either E or Z stereochemistry where applicable. This term would include, for example, vinyl, 1-propenyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

The term "cycloalkyl" refers to a saturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclohexyl, cyclooctyl, cycloheptyl, cyclopentyl, cyclobutyl and cyclopropyl.

The term "cycloalkenyl" refers to an unsaturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclohexenyl, cyclooctenyl, cycloheptenyl, cyclopentenyl, cyclobutenyl and cyclopropenyl. In the case of cycloalkenyl rings of from 5-8 carbon atoms, the ring may contain more than one double bond.

The term "heterocyclyl" or "heterocyclic" refers to a 5-7 membered heterocyclic ring containing one or more heteroatoms selected from S, N and O, and optionally fused to a benzene ring, including for example, pyrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperizinyl, indolyl and benzimidazole.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four substituents, each of which independently may be C_1-C_6 alkoxy, hydroxy, thio, C_1-C_6 alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, nitro, -COOH, -$CONH_2$ or -$CONHR^A$ wherein R^A is a C_1-C_6 alkyl group or the residue of a natural alpha-amino acid.

The term "characteristic side chain of a natural alpha-amino acid" means the characteristic side chain attached to the -$CH(NH_2)(COOH)$ moiety in the following amino acids: glycine, alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid and aspartic acid.

Where a carboxylic acid group is esterified in compounds of formula (I), the

notional esterifying moiety may be, for example, a C_1-C_6 alkanol or benzyl alcohol.

Where a carboxylic acid group is amidated in compounds of formula (I), examples include aminocarbonyl, (C_1-C_6 alkyl)aminocarbonyl, di(C_1-C_6 alkyl)aminocarbonyl, and benzylaminocarbonyl groups, as well as carboxylic acid groups amidated with an aminocarboxylic acid such as a natural alpha amino acid (eg glycine, alanine etc).

Salts of the compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases, for example sodium, potassium, magnesium, and calcium salts.

There are several chiral centres in the compounds according to the invention because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereomers with R or S stereochemistry at each chiral centre. General formula (I), and (unless specified otherwise) all other formulae in this specification are to be understood to include all such stereoisomers and mixtures (for example racemic mixtures) thereof.

In the compounds of the invention, the preferred stereochemistry is in general as follows:

C atom carrying the hydroxy group and hydroxamic acid moiety - S,
C atom carrying the R_2 group - R,
C atom carrying the R_3 group - S,

but mixtures in which the above configurations predominate are also contemplated.

In the compounds of the invention:

R_2 may for example be a C_3-C_6 alkyl, cycloalkyl(C_3-C_6 alkyl), phenyl(C_2-C_6 alkyl), C_2-C_4 alkoxy(C_1-C_3 alkyl)$_m$, or C_2-C_4 alkylsulphanyl(C_1-C_3 alkyl)$_m$ group wherein is 0 or 1. Examples of particular R_2 groups include iso-butyl, n-pentyl, cyclohexylpropyl, cyclohexylbutyl, cyclohexylpentyl, phenylethyl,

phenylpropyl, phenylbutyl, phenylpentyl, propyloxymethyl, and propylsulphanyl. Presently preferred are compounds in which R_2 is iso-butyl;

(always subject to the proviso that R_3 is not the characteristic side chain of a natural alpha-amino acid, or the characteristic side chain of a natural alpha-amino acid in which any functional substituents are protected, any amino groups are acylated, and any carboxyl groups are esterified), R_3 may for example be a phenyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, phenyl(C_1-C_6 alkyl), substituted phenyl(C_1-C_6 alkyl), cycloalkyl, cycloalkyl(C_1-C_6 alkyl), thienyl, thienyl(C_1-C_6 alkyl), pyridyl(C_1-C_6 alkyl), thiazolyl(C_1-C_6 alkyl), thiofuranyl(C_1-C_6 alkyl), benzothiofuranyl(C_1-C_6 alkyl) or imidazolyl(C_1-C_6 alkyl) group, or R_3 and R_5 taken together may form a C_7-C_{12} alkylene chain, optionally interrupted by an O, S or N heteroatom. Examples of particular R_3 groups include phenyl, t-butyl, cyclohexylpropyl, cyclohexylbutyl, cyclohexylpentyl, optionally substituted phenylethyl, phenylpropyl, phenylbutyl and phenylpentyl in which the optional substituent(s) are in the phenyl ring and are selected from phenyl, hydroxy, C_1-C_6 alkoxy, benzyloxy, tetrafluoromethyl, halo (eg chloro) and R_8-(C=O)-(C_1-C_6alkyl)-O- wherein R_8 is hydroxy, amino, or an amino acid residue linked via an amide bond. Other examples of particular R_3 groups include phenylethyl, cyclohexyl, thienyl(C_1-C_6 alkyl), pyridylmethyl, thiazolylmethyl, thiofuranylmethyl, benzothiofuranylmethyl or imidazolylmethyl, 1-ethenyl, 1-propenyl, 1-propynyl, 2,2-dimethylpropyl, napthyl, napthylmethyl, propyloxymethyl, butyloxymethyl, and propylsulphanylmethyl, and butylsulphanylmethyl. Presently preferred are compounds in which R_3 is cyclohexylmethyl, t-butyl, 2-thienylmethyl, (4-hydroxycarbonylmethoxy)-phenylmethyl, (4-phenyl)phenylmethyl, methoxycarbonylethyl, and N-hydroxyaminocarbonylethyl;

R_4 may for example be hydrogen, methyl or ethyl. Presently preferred are compounds in which R_4 is hydrogen;

R_5 may for example be hydrogen or C_1-C_4 alkyl, or a group D-(C_1-C_6 alkyl)

wherein D represents hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, acylamino, optionally substituted phenyl, or a heterocyclic group. Examples of particular R_5 groups include methyl, ethyl, propyl, butyl, hydroxyethyl, 2-ethylthioethyl, 2-acetoxyethyl, N-acetyl-2-aminoethyl, 3-(2-pyrrolidone)propyl, optionally substituted phenylethyl, phenylpropyl, phenylbutyl and phenylpentyl, Presently preferred are compounds in which R_5 is methyl or ethyl.

Interesting compounds of the invention are:

N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy) phenylalanine-N^1-methylamide;
N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-phenylglycine-N^1-methylamide;
N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-(4-phenyl)-phenylalanine-N^1-methylamide;
N^3-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]amino-1-azacyclotridecan-2-one;
N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-(1-pyrazolyl) alanine-N^1- methylamide;
N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-4-(N-hydroxyamino)glutamic acid-N^1-methylamide;
N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-(2-thienyl) alanine-N^1- methylamide;
N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-cyclohexyl alanine-N^1-(3-(2-pyrrolidone)propyl)amide,

and salts, solvates or hydrates thereof.

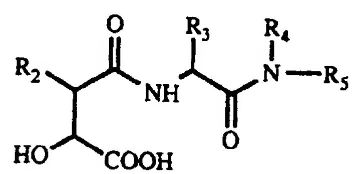
Compounds of the invention which are presently especially preferred for their balance of good formulation characteristics such as water solubility, high intrinsic activity in inhibiting collagenase and stromelysin, activity in inhibiting TNF release, and good pharmacokinetic properties, evidenced for example by high *in vivo* activity following oral administration in the standard rat adjuvant arthritis model, are:

N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-cyclohexyl alanine-N^1 methylamide;
N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-tert-leucine-N^1-methylamide,

and salts, solvates or hydrates thereof.

Compounds according to the present invention may be prepared by methods known *per se* in the art, and by the following process, which forms another aspect of the invention, namely a process for the preparation of a compound of formula (I) comprising:

(a) coupling an acid of general formula (II)


(II)

or an activated derivative thereof with hydroxylamine, O-protected hydroxylamine, or a salt thereof, R_2, R_3, R_4 and R_5 being as defined in general formula (I) except that any substituents in R_2, R_3, R_4 and R_5 which are potentially reactive with hydroxylamine, O-protected hydroxylamine or their salts may themselves be protected from such reaction, then removing any protecting groups from the resultant hydroxamic acid moiety and from any protected substituents in R_2, R_3, R_4 and R_5; and

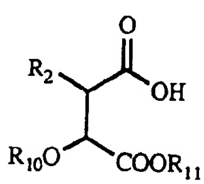
(b) optionally converting a compound of general formula (I) into another compound of general formula (I).

Conversion of (II) to an activated intermediate such as the pentafluorophenyl, hydroxysuccinyl, or hydroxybenzotriazolyl ester may be effected by reaction with the appropriate alcohol in the presence of a dehydrating agent such as dicyclohexyl dicarbodiimide (DCC), N,N-dimethylaminopropyl-N'-ethyl

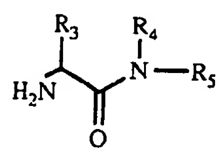
carbodiimide (WSCDI), or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ).

Protecting groups as referred to above are well known per se, for example from the techniques of peptide chemistry. Amino groups are often protectable by benzyloxycarbonyl, t-butoxycarbonyl or acetyl groups, or in the form of a phthalimido group. Hydroxy groups are often protectable as readily cleavable ethers such as the t-butyl or benzyl ether, or as readily cleavable esters such as the acetate. Carboxy groups are often protectable as readily cleavable esters, such as the t-butyl or benzyl ester.

A compound of general formula (II) can be prepared by coupling an acid of formula (III) or an activated derivative thereof with an amine of formula (IV)

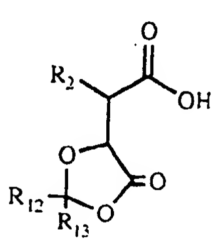


(III)



(IV)

wherein R_2, R_3, R_4, and R_5 are as defined in general formula (I) and R_{10} and R_{11} separately represent hydroxy protecting groups or taken together represent a divalent moeity which simultaneously protects both hydroxy groups, and subsequently removing the protecting groups or protecting moeity. Active derivatives of acids (III) include activated esters such as the pentafluorophenyl ester, acid anhydrides and acid halides, eg chlorides. R_{10} and R_{11} may be any of the standard hydroxyl protecting groups known in the art, but a particularly useful technique may be simultaneous protection of the two hydroxy groups as a dioxalone of formula (V):



(V)

wherein the groups R_{12} and R_{13} are derived from a dioxalone forming reagent, and may be, for example, hydrogen, alkyl, phenyl or substituted phenyl.

As mentioned above, compounds of formula (I) are useful in human or veterinary medicine since they are active as inhibitors of MMPs, and a further advantage lies in their ability to inhibit the release of tumour necrosis factor (TNF) from cells.

Accordingly in another aspect, this invention concerns:

(i) a method of management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs and/or TNF in mammals, in particular in humans, which method comprises administering to the mammal an effective amount of a compound as defined with respect to formula (I) above, or a pharmaceutically acceptable salt thereof; and

(ii) a compound as defined with respect to formula (I) for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs and/or TNF; and

(iii) the use of a compound as defined with respect to formula (I) in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs and/or TNF.

Diseases or conditions mediated by MMPs include those involving tissue breakdown such as bone resorption, inflammatory diseases, dermatological conditions and tumour invasion by secondary metastases, in particular rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration and tumour invasion by secondary metastases. Diseases or conditions mediated by TNF include inflammation, fever, cardiovascular effects, haemorrhage, coagulation and acute phase response, cachexia and anorexia, acute infections, shock states, graft versus host reactions and autoimmune disease.

In a further aspect of the invention there is provided a pharmaceutical or veterinary

composition comprising a compound of formula (I) together with a pharmaceutically or veterinarily acceptable excipient or carrier. In view of the water-solubility, and oral bioavailability advantanges of compounds in accordance with the invention, a further aspect of the invention comprises a pharmaceutical or veterinary composition comprising a compound of formula (I) together with a pharmaceutically or veterinarily acceptable excipient or carrier, characterised in that the composition is adapted for oral administration.

One or more compounds of general formula (I) may be present in the composition together with one or more excipient or carrier.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. The orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

The dosage unit involved in oral administration may contain from about 1 to 250mg, preferably from about 25 to 250mg of a compound of the invention. A suitable daily dose for a mammal may vary widely depending on the condition of the patient. However, a dose of a compound of general formula I of about 0.1 to 300mg/kg body weight, particularly from about 1 to 100mg/kg body weight may be appropriate.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

For topical application to the eye, the drug may be made up into a solution or suspension in a suitable sterile aqueous or non aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite os disodium edeate; preservatives including bactericidal and fungicidal agents such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

The dosage for topical administration will of course depend on the size of the area being treated. For the eyes, each dose may typically be in the range from 10 to 100mg of the drug.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

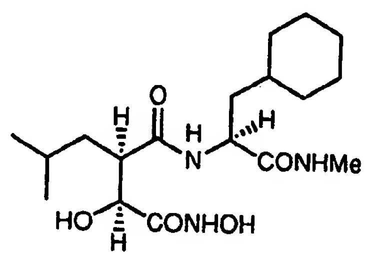
For use in the treatment of rheumatoid arthritis, the drug can be administered by the oral route or by injection intra-articularly into the affected joint. The daily dosage for a 70kg mammal may be in the range 10mgs to 1gram.

The following Examples illustrate embodiments of the invention:

The amino acids used in the examples below were commercially available or were prepared according to literature procedures. In all cases these were converted to the required N-methylamides by standard methods.

Example 1

N2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-cyclohexyl alanine-N1 methylamide



Example 1a

Isopropyl 3R-carboxyisopropyl-2S-hydroxy-5-methylhex-5-enoate

Diisopropyl-2S-hydroxybutanedioate (50 g, 230 mmol) was added to a solution of lithium N,N-diisopropylamide [from N,N-diisopropylamine (80 ml, 570 mmol) and 10M n-butyllithium (48.1 ml, 481 mmol)] in dry tetrahydrofuran (500 ml) whilst maintaining the temperature at -70°C. When addition was complete the reaction was warmed to -15°C and stirred for 8 hours. The reaction mixture was cooled to -70°C and methallyl iodide (46 g, 252 mmol) was added slowly, ensuring that the temperature did not exceed -65°C. The mixture was warmed to -40°C and stirred for 18 hours before quenching at -15°C with citric acid. The organic layer was separated and washed with 10% sodium bicarbonate solution (500 ml) and brine (300 ml) then dried over magnesium sulphate. The solution was filtered and concentrated *in vacuo* to give a brown oil (64 g) which was purified by column chromatography (silica gel, 1 kg, gradient elution with 20 to 35% diethyl ether in hexane). The desired product was isolated as a colourless oil (30.9 g, 49%) which was found to be a 17:1 mixture of diastereomers by NMR. ^{1}H-NMR; δ (Chloroform-d, major diastereomer), 5.06 (1H, septet, J=6.3 Hz), 4.97 (1H, septet, J=6.3 Hz),

4.78 (2H, d, J=7.1 Hz), 4.16 (1H, m), 3.20 (1H, d, J=6.2 Hz), 3.00 (1H, m), 2.50, 2.35 (2H, ABX, J=7.0, 8.7, 14.4 Hz), 1.72 (3H, s) and 1.24 - 1.16 (12H, 2m).

Example 1b

Isopropyl 3R-carboxyisopropyl-2S-hydroxy-5-methylhexanoate

Isopropyl 3R-carboxyisopropyl-2S-hydroxy-5-methylhex-5-enoate (7.14 g, 26.2 mmol) was dissolved in ethanol (80 ml), and stirred overnight with 10% palladium on charcoal catalyst (1.0 g) under an atmosphere of hydrogen. The catalyst was removed by filtration and the filtrate was evaporated to dryness to leave the product as a clear oil (7.03 g, 98%). ^{1}H-NMR; δ (Chloroform-d), 5.06 (1H, septet, J=6.3 Hz), 4.97 (1H, septet, J=6.3 Hz), 4.17 (1H, br s,), 3.24 (1H, br s), 2.83 (1H, m), 1.68 (2H, m), 1.44 (1H, m), 1.24 (6H, d, J=6.2 Hz), 1.18 (6H, d, J=6.2 Hz) and 0.89 (6H, m).

Example 1c

3R-Carboxy-2S-hydroxy-5-methylhexanoic acid

Isopropyl 3R-Carboxyisopropyl-2S-hydroxy-5-methylhexanoate (7.0 g, 25.6 mmol) was dissolved in dioxane (15 ml) and water (15 ml), a solution of potassium hydroxide (4.29 g) in water (22 ml) was added and the mixture was heated at 90°C overnight. The solution was allowed to cool and then passed through an ion exchange resin (Dowex 50X4-400, 200 ml) to yield the title compound (4.82 g, 99%). ^{1}H-NMR; δ (Chloroform-d), 8.70 (2H, br s), 4.32 (1H, br s), 3.10 (1H, m), 1.85 - 1.55 (3H, m) and 0.96 (6H, m).

Example 1d

2R-(2,2-Dimethyl-4-oxo-1,3-dioxalan-5S-yl)-4-methylpentanoic acid

3R-Carboxy-2S-hydroxy-5-methylhexanoic acid (5.19 g, 27.3 mmol) was dissolved in 2,2-dimethoxypropane (150 ml) and N,N-dimethylformamide (40 ml) and stirred overnight at 30°C in the presence of a catalytic amount of p-toluene sulphonic acid. The solvent was removed to give the title compound contaminated with solvent (6.87 g, >100%). ^{1}H-NMR; δ (Chloroform-d), 4.41 (1H, d, J=4.8 Hz), 2.91 (1H, m), 1.69 (3H, m), 1.54 (3H, s), 1.48 (3H, s) and 0.88 (6H, m).

Example 1e

Pentafluorophenyl R-(2,2-Dimethyl-4-oxo-1,3-dioxalan-5S-yl)-4-methyl pentanoate

2R-(2,2-Dimethyl-4-oxo-1,3-dioxalan-5S-yl)-4-methylpentanoic acid (558 mg, 2.4 mmol) was taken up in dichloromethane (10 ml) and cooled to 0°C before adding pentafluorophenol (670 mg, 3.6 mmol) and N-ethyl-N'-(3-dimethylaminopropyl) carbodiimide (560 mg, 2.9 mmol). The reaction was stirred at 0°C for 2 hours then the solution was washed with 1M sodium carbonate (50 ml) and brine (20 ml). The organic layer was dried (magnesium sulphate), filtered, evaporated to dryness and purified by column chromatography (silica gel, dichloromethane) to give the activated ester (552 mg, 58%). ^{1}H-NMR; δ (Chloroform-d), 4.57 (1H, d, J=6.5 Hz), 3.32 (1H, m), 1.86 (3H, m), 1.67 (3H, s), 1.58 (3H, s) and 1.03 (6H, m).

Example 1f

N^2-[2R-(2,2-Dimethyl-4-oxo-1,3-dioxalan-5S-yl)-4-methylpentanoyl]-L-cyclohexyl alanine-N^1-methylamide

Pentafluorophenyl 2R-(2,2-dimethyl-4-oxo-1,3-dioxalan-5S-yl)-4-methyl pentanoate (1.06 g, 2.7 mmol) and L-cyclohexylalanine-N-methylamide (0.33 g, 1.8 mmol) were dissolved in N,N-dimethylformamide (150 ml) and the mixture was

stirred overnight at room temperature. The solvent was removed to give an oil which was purified by column chromatography (silica gel, gradient elution with 0 to 5% methanol in dichloromethane) gave first unreacted ester followed by the desired product (0.43 g, 60%). ^{1}H-NMR; δ (Chloroform-d), 6.47 (2H, br m and d, J=8.3 Hz), 4.53 (1H, d, J=6 Hz), 4.49 (1H, m), 2.76 (4H, m), 1.80 - 1.50 (12H, br m), 1.62 (3H, s), 1.54 (3H, s), 1.35 - 1.10 (4H, br m) and 0.91 (6H, m).

Example 1g

N^2-[3S-Hydroxy-4-hydroxy-2R-isobutylsuccinyl]-L-cyclohexylalanine-N^1-methylamide.

N^2-[2R-(2,2-Dimethyl-4-oxo-1,3-dioxalan-5S-yl)-4-methylpentanoyl]-L-cyclohexyl alanine-N^1-methylamide (0.43 g, 1.1 mmol) was dissolved in 2M hydrochloric acid (15 ml) and tetrahydrofuran (20 ml) and stirred at room temperature overnight. The solvent was removed to give the required product as an off white foam (0.35 g, 91%). ^{1}H-NMR; δ (Methanol-d_4), 4.37 (1H, m), 4.16 (1H, d, J=5.6 Hz), 2.75 (1H, m), 2.68 (3H, s), 1.80 - 1.50 (12H, m), 1.38 - 1.10 (4H, br m) and 0.90 (6H, m).

Example 1h

N^2-[4-(N-Benzyloxyamino)-3S-hydroxy-2R-isobutylsuccinyl]-L-cyclohexylalanine-N^1- methylamide.

N^2-[3S-Hydroxy-4-hydroxy-2R-isobutylsuccinyl)]-L-cyclohexylalanine-N^1-methylamide (0.35 g, 1.0 mmol) was taken up in tetrahydrofuran (5 ml) then water (5 ml) and O-benzylhydroxylamine hydrochloride (0.24 g, 1.5 mmol) was added. The solution was cooled to 0°C before addition of N-ethyl-N'-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.38 g, 2.0 mmol) and the reaction mixture was then stirred at room temperature overnight. Tetrahydrofuran was removed under reduced pressure, whereupon the product crystallised. The

mixture was diluted with an equal volume of water and the product was collected by filtration, washed with water and dried under high vaccuum (0.30 g, 65%). ^{1}H-NMR; δ (Methanol-d_4), 7.50 - 7.30 (5H, m), 4.81 (2H, s; under H_20 peak), 4.36 (1H, t, J=7.6 Hz), 3.98 (1H, d, J=6.1 Hz), 2.72 (1H, m), 2.67 (3H, s), 1.85 - 1.43 (12H, br m), 1.38 - 1.10 (4H, br m) and 0.88 (6H, m).

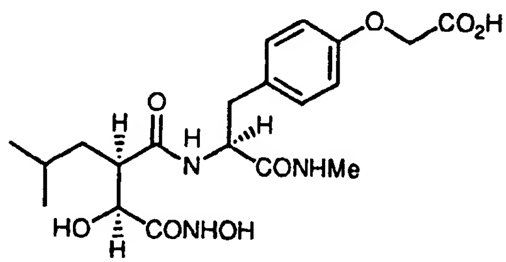
Example 1i

N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-cylohexylalanine-N^1-methylamide.

N^2-[4-(N-Benzyloxyamino)-2S-hydroxy-2R-isobutylsuccinyl)]-L-cyclohexylalanine-N^1-methylamide (1.0 g, 2.16 mmol) was dissolved in ethanol (100 ml), 10% palladium on charcoal (100 mg) was added and the mixture was subjected to an atmosphere of hydrogen. After 4 hours the catalyst was filtered off then the solvent removed to give the title compound (650 mg, 1.75 mmol, 81%) : ^{1}H-NMR; δ (Methanol-d_4), 4.35 (1H, t, J=7.6 Hz), 3.99 (1H, d, J=6.4 Hz), 2.69 (4H, m and s), 1.80 - 1.50 (12H, br m), 1.40 - 1.10 (4H, br m) and 0.89 (6H, m). ^{13}C-NMR; δ (Methanol-d_4), 175.6, 175.3, 171.5, 72.9, 52.4, 40.2, 39.2, 35.2, 34.9, 33.2, 30.9, 27.6, 27.4, 27.1, 26.9, 26.3, 23.7 and 22.1. Found: C, 58.27, H, 8.93, N, 11.20% ; $C_{18}H_{33}N_3O_5$ requires: C, 58.20, H, 8.95, N, 11.31%.

Example 2

N2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy) phenylalanine-N1-methylamide.



Example 2a

Methyl 3R-carboxy-2S-hydroxy-5-methylhexanoate.

3R-Carboxy-2S-hydroxy-5-methylhexanoic acid (5.76g, 30.3 mmol), prepared by the method described in Example 1c, was cooled to 0°C and treated with trifluoroacetic anhydride (14 ml). The mixture was stirred for 2 hours then the excess anhydride was removed under reduced pressure. The resulting brown oil was dissolved in freshly distilled anhydrous methanol (30 ml) and stirred overnight. The solution was evaporated to give the crude product (7.0 g, >100%) which was used without further purification. ^{1}H-NMR; δ (Chloroform-d), 4.28 (1H, d, J=6 Hz), 3.80 (3H, s), 3.00 (1H, dt, J=6, 8 Hz), 1.73 (2H, m), 1.54 (1H, m), and 0.96 (6H, m). ^{13}C-NMR; δ (Chloroform-d), 176.2, 172.5, 69.6, 51.3, 45.0, 35.3, 24.2, and 20.9.

Example 2b

N2-[3S-Hydroxy-2R-isobutyl-4-methoxysuccinyl]-L-(4-oxymethylcarboxy benzyl)phenylalanine-N1-methylamide

Methyl 3R-carboxy-2S-hydroxy-5-methylhexanoate (700 mg, 3.4 mmol), 4-(oxy methylcarboxybenzyl)-L-phenylalanine-N-methylamide (1.56 g, 4.56 mmol),

pentafluorophenol (1.26 g, 6.8 mmol) and N-methylmorpholine (690 mg, 6.8 mmol) were dissolved in dimethylformamide (30 ml) and cooled to 0°C before addition of N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (980 mg, 5.1 mmol). After stirring overnight at room temperature the solvent was removed under reduced pressure and the residue was purified by column chromatography (C30 silica gel, gradient elution with 50 to 100% ethyl acetate in hexane). The desired product was isolated as a pale yellow solid (1.42 g, 78%). ^{1}H-NMR; δ (Chloroform d), 7.34 (5H, s), 7.09 (2H, d, J = 8 Hz), 6.92 (1H, d, J = 8 Hz), 6.79 (2H, d, J = 8 Hz), 6.55 (1H, q, J = 6 Hz), 5.20 (2H, s), 4.60 (3H, m), 4.22 (1H, d, J = 4 Hz), 3.71 (3H, s), 3.00 (2H, m), 2.76 (1H, m), 2.48 (3H, d, J = 6 Hz), 1.55 (1H, m), 1.42 (2H, m), 0.88 (3H, d, J = 7 Hz), and 0.88 (3H, d, J = 7 Hz). ^{13}C-NMR; δ (Chloroform-d), 172.6, 172.3, 171.7, 170.3, 134.3, 127.1, 126.9, 127.8, 70.4, 65.1, 51.0, 50.8, 46.1, 36.6, 28.9, 26.2, 24.8, 24.2, 21.1, and 21.0.

Example 2c

N^2-[4-(N-Benzyloxyamino)-3S-hydroxy-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy benzyl) phenylalanine-N^1-methylamide.

N^2-[3S-Hydroxy-2R-isobutyl-4-methoxysuccinyl]-L-(4-oxymethylcarboxybenzyl) phenylalanine-N^1-methylamide (820 mg, 1.55 mmol) was dissolved in tetrahydrofuran (7 ml) and water (7 ml), lithium hydroxide (66 mg, 1.55 mmol) was added and the solution was stirred overnight at ambient temperature. Evaporation of the solvents under reduced pressure gave the carboxylic acid lithium salt which was characterised by ^{1}H NMR. The salt was redissolved in tetrahydrofuran (15 ml) and water (15 ml) and treated with O-benzylhydroxylamine hydrochloride (0.30 g, 1.86 mmol) followed by N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.36 g, 1.86 mmol). After stirring overnight at room temperature the tetrahydrofuran was removed to leave an oil which was extracted several times with ethyl acetate. The combined organic solutions were dried (magnesium sulphate), filtered and concentrated. Further purification by column chromatography (C30 silica gel, ethyl acetate) gave the title compound as a white

solid (213 mg, 22%). ^{1}H-NMR; δ (Methanol-d_4), 7.80 (1H, d, J = 8 Hz), 7.41 (2H, m), 7.32 (8H, m), 7.19 (2H, d, J = 8 Hz), 6.78 (2H, d, J = 8 Hz), 5.17 (2H, s), 4.80 (4H, m), 4.50 (1H, dd, J = 7, 8 Hz), 3.99 (1H, d, J = 4 Hz), 3.07 (1H, dd, J = 14, 6 Hz), 2.88 (1H, dd, J = 14, 8 Hz), 2.64 (4H, m and s), 1.46 (1H, m), 1.29 (1H, m), 1.12 (1H, m), and 0.80 (6H, t, J=7 Hz).

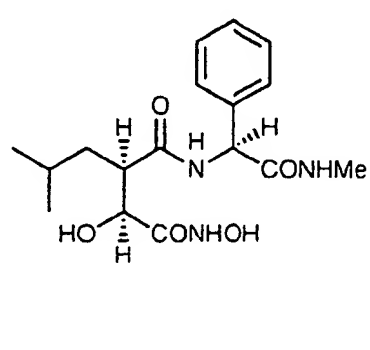
Example 2d

N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxy)phenylalanine-N^1-methylamide.

N^2-[4-(N-Benzyloxyamino)-3S-hydroxy-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy benzyl)phenylalanine-N^1-methylamide (210 mg, 0.34 mmol) was dissolved in ethanol (35 ml) and hydrogenated over 10% palladium on charcoal (200 mg) for one hour. The catalyst was removed by filtration and the solvent was removed to give the desired compound (140 mg, 93%): ^{1}H-NMR; δ (Methanol-d_4), 7.1 (2H, d, J=8.5 Hz), 6.8 (2H, d, J=8.5 Hz), 4.5 (2H, s), 4.4 (1H, dd, J=8.2, 6.7 Hz), 4.01 (1H, d, J=5.6 Hz), 3.05 (2H, dd, J=12.9, 6.2 Hz), 2.90 (2H, dd, J=13.9, 8.3 Hz), 2.61 (1H, m), 2.60 (3H, s), 1.3 (3H, m), and 0.8 (6H, t, J=6.3 Hz). ^{13}C-NMR; δ (Methanol-d_4), 175.5, 173.9, 171.5, 158.5, 131.3, 131.1, 115.7, 72.7, 66.7, 58.3, 56.3, 39.3, 37.9, 26.6, 26.4, 23.8, 22.1, and 18.4.

Example 3

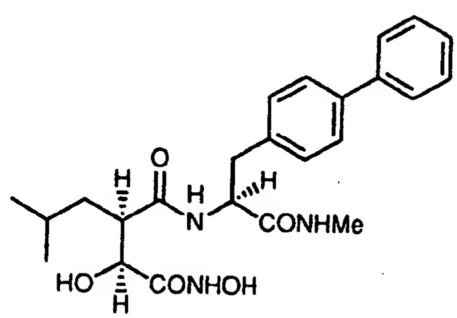
N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-phenylglycine-N^1-methylamide



Prepared in a manner analogous to that described in example 1, from L-phenylglycine-N-methylamide. ^{1}H-NMR; δ (Methanol-d_4), 7.37 (5H, m), 5.4 (1H, s), 4.05 (1H, d, J=5 Hz), 3.1 (1H, m), 2.7 (3H, s), 1.6 (2H, m), 1.27 (1H, m), 0.9 (6H, 2d, J=6 Hz). ^{13}C-NMR; δ (Methanol-d_4), 175.3, 172.9, 171.5, 139.0, 129.7, 129.1, 128.5, 73.0, 58.7, 43.4, 39.1, 26.8, 26.5, 23.6, 22.3.

Example 4

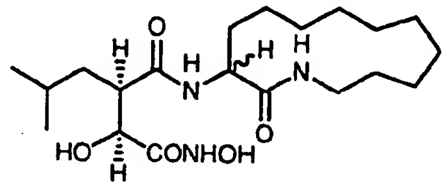
N2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-(4-phenyl)-phenylalanine-N1-methylamide.



Prepared in a manner analogous to that described in Example 1, from L-(4-phenyl) phenylalanine-N-methylamide: ^{1}H-NMR; δ (Dimethyl sulphoxide-d_6), 7.90 (2H, m), 7.62 (2H, d, J=7.9 Hz), 7.46 (6H, m), 7.30 (2H, d, J=7.9Hz), 5.66 (1H, br s), 4.44 (1H, m), 3.86 (1H, d, J=6.9 Hz), 3.12 (1H, dd, J=5.2, 13.8 Hz), 2.93 (1H, dd, J=9.1, 13.8 Hz), 2.58 (3H, d, J=4.3 Hz), 2.51 (1H, m), 1.40 (1H, m), 1.24 (1H, m) 1.19 (1H, br m), 0.94 (1H, m) and 0.72 (6H, m). ^{13}C-NMR; δ (Dimethyl sulphoxide-d_6), 172.5, 171.1, 168.7, 140.1, 138.0, 137.5, 129.6, 128.9, 127.2, 126.4, 126.3, 71.2, 54.1, 48.3, 37.4, 36.6, 25.6, 25.0, 23.6 and 21.5. Found: C, 63.43, H, 7.00, N, 8.92% ; $C_{24}H_{31}N_3O_5.0.7H_20$ requires: C, 63.48, H, 7.19, N, 9.25%

Example 5

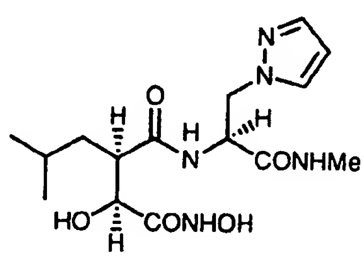
N3-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]amino-1-azacyclotridecan-2-one



Prepared in a manner analogous to that described in Example 1, from 3(RS)-amino-1 azacyclotridecan-2-one: ^{1}H-NMR; δ (Dimethyl sulphoxide-d_6), 10.60 (1H, d, J=10.7 Hz), 8.86 (1H, d, J=7.9 Hz), 7.83 (1H, d, J=7.3 Hz), 7.61 (1H, d, J=7.6 Hz), 5.46 (0.5 H, d, J=6.4 Hz; diastereomer A), 5.31 (0.5 H, d, J =7.5 Hz; diastereoisomer B), 4.22 (1H, m), 3.72 (1H, d, J=7.4 Hz), 2.98 (1H, br m), 2.78 (2H, br m), 1.6 - 1.25 (21H, br m) and 0.82 (6H, m). ^{13}C-NMR; δ (Dimethyl sulphoxide-d_6), 175.5, 173.9, 171.5, 73.4, 55.4, 54.9, 40.0, 39.5, 39.0, 32.7, 29.3, 27.7, 27.1, 26.8, 26.1, 25.4, 24.6, 23.6, 23.0 and 22.3.

Example 6

N2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-(1-pyrazolyl) alanine-N1- methylamide

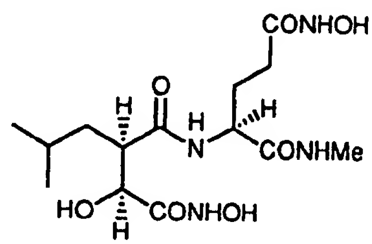


Prepared in a manner analogous to that described in Example 1, from L-3-(1 pyrazolyl)alanine-N-methylamide. ^{1}H-NMR; δ (Dimethyl sulphoxide-d_6), 10.70 (1H, s), 8.93 (1H, s), 8.00 (2H, m), 7.59 (1H, d, J=2 Hz), 7.41 (1H, d, J=1.5 Hz), 6.22 (1H, m), 5.75 (1H, d, J=5.8 Hz), 4.57 (1H, m), 4.46 (2H, m), 3.86 (1H, dd, J=6.2 Hz), 2.55

(4H, m), 1.44 (1H, m), 1.25 (1H, m), 0.97 (1H, m) and 0.76 (6H, m). [13]C-NMR; δ (Dimethyl sulphoxide-d_6), 172.7, 169.2, 168.6, 138.9, 130.6, 104.9, 71.1, 53.6, 51.6, 48.4, 37.1, 25.7, 25.0, 23.6 and 21.5. Found: C, 50.11, H, 7.01, N, 8.92% ; $C_{15}H_{25}N_5O_5.0.2H_20$ requires: C, 50.19, H, 7.13, N, 19.51%

Example 7

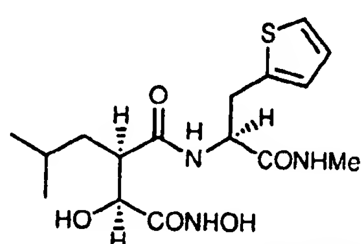
N[2]-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-4-(N-hydroxyamino)glutamic acid-N[1]-methylamide



Prepared in a manner analogous to that described in Example 1, from 5-methyl-L glutamic acid N-methylamide. [1]H-NMR; δ (Dimethyl sulphoxide-d_6), 10.64 (1H, br s), 10.30 (1H, br s), 8.9 (1H, br s), 8.7 (1H, br s), 7.8 (1H, d, J = 8 Hz), 7.72 (1H, d, J = 4.5 Hz), 5.35 (1H, d, J = 6.9 Hz), 4.16 (1H, m), 3.75 (1H, m), 2.57 (4H, d and m), 2.14 - 1.73 (4H, br m), 1.44 (3H, br m), and 0.80 (6H, m). [13]C-NMR; δ (Dimethyl sulphoxide-d_6), 172.8, 171.4, 168.7, 168.6, 71.3, 52.3, 47.7, 37.2, 28.9, 28.0, 25.5, 25.2, 23.6 and 21.7.

Example 8

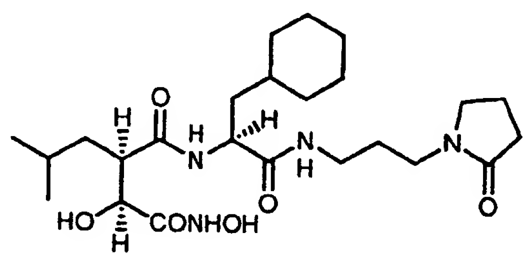
N[2]-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-(2-thienyl) alanine-N[1]- methylamide



Prepared in a manner analogous to that described in Example 1, from L-3-(2 thienyl)alanine-N-methylamide. [1]H-NMR; δ (Methanol-d_4), 7.18 (1H, d, J=4.8 Hz), 6.88 (2H, dd, J=3.5, 4.8 Hz), 4.49 (1H, dd, J=7.0 Hz), 4.01 (1H, d, J=5.4 Hz), 3.27 (2H, m), 2.67 (4H, m), 1.53 (1H, m), 1.33 (1H, m), 1.24 (1H, m) and 0.82 (6H, m). [13]C-NMR; δ (Methanol-d_4), 175.6, 173.3, 171.4, 140.2, 127.8, 127.5, 125.3, 72.7, 56.2, 39.2, 32.6, 26.6, 26.4, 23.7, 22.1 and 21.9.

Example 9

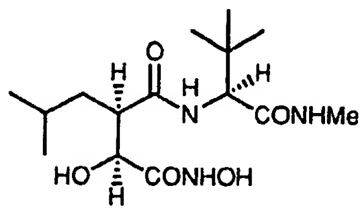
N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-cyclohexyl alanine-N^1-(3-(2-pyrrolidone)propyl)amide



Prepared in a manner analogous to that described in Example 1, from L-cyclohexylalanine-N-(3-(2-pyrrolidone)propyl)amide: [1]H-NMR; δ (Methanol-d_4), 4.35 (1H, m), 4.01 (1H, d, J=6.3 Hz), 3.43 (2H, m), 3.27 (2H, m), 3.15 (2H, m), 2.73 (1H, m), 2.34 (2H, t, J=7.8 Hz), 2.01 (2H, m), 1.70 (15H, br m), 1.21 (3H, br m) and 0.90 (6H, dd, J=5.3, 6.3 Hz). [13]C-NMR; δ (Methanol-d_4), 177.9, 175.7, 174.8, 171.5, 73.0, 52.7, 41.2, 40.3, 39.3, 37.8, 35.4, 34.9, 33.2, 32.0, 27.8, 27.6, 27.4, 27.1, 26.9, 23.8, 22.3 and 18.9. Found: C, 60.06, H, 8.88, N, 11.60% ; $C_{24}H_{42}N_4O_6$ requires: C, 59.73, H, 8.77, N, 11.61%.

Example 10

N2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-tert-leucine-N1-methylamide



Prepared in a manner analogous to that described in Example 1, from L-tert-leucine-N methylamide: ^{1}H-NMR; δ (Methanol-d_4), 4.17 (1H, s), 4.00 (1H, d, J=5.6 Hz), 2.81 (1H, m), 2.69 (3H, s), 1.65 - 1.44 (2H, br m), 1.29 - 1.21 (1H, br m), 0.95 (9H, s), 0.88 (3H, d, J=6.5 Hz) and 0.86 (3H, d, J=6.5 Hz). ^{13}C-NMR; δ (Methanol-d_4), 175.4, 173.2, 171.5, 73.0, 62.1, 39.8, 35.4, 27.2, 26.9, 26.0, 23.5 and 22.4. Found: C, 54.36, H, 8.74, N, 12.73% ; $C_{15}H_{29}N_2O_5$ requires: C, 54.36, H, 8.82, N, 12.68%.

Biological Example A

The potency of compounds of the invention as inhibitors of collagenase was determined by the procedure of Cawston and Barrett, (Anal. Biochem., **99**, 340-345, 1979), hereby incorporated by reference, whereby a 1mM solution of the compound being tested, or a dilution thereof, was incubated at 37° for 16 hours with collagen and collagenase (buffered with 25mM Hepes, pH 7.5 containing 5mM $CaCl_2$, 0.05% Brij 35 and 0.02% NaN_3). The collagen was acetylated ^{14}C collagen prepared by the method of Cawston and Murphy, (Methods in Enzymology, **80**, 711, 1981), hereby incorporated by reference. The samples were centrifuged to sediment undigested collagen, and an aliquot of the radioactive supernatant removed for assay on a scintillation counter as a measure of hydrolysis. The collagenase activity in the presence of 1mM of the test compound, or a dilution thereof, was compared to activity in a control devoid of inhibitor and the result reported below as that of inhibitor concentration effecting 50% inhibition of the collagenase activity (IC_{50}).

The potency of compounds of the invention as inhibitors of stromelysin was determined by the procedure of Cawston et al, (Biochem. J., **195**, 159-165, 1981), hereby incorporated by reference, whereby a 1mM solution of the compound being tested, or a dilution thereof, was incubated at 37° for 16 hours with stromelysin and ^{14}C acetylate casein (buffered with 25mM Hepes, pH 7.5 containing 5mM $CaCl_2$, 0.05% Brij 35 and 0.02% NaN_3). The casein was acetylated ^{14}C casein prepared by the method of Cawston et al (ibid). The stromelysin activity in the presence of 1mM of the test compound, or a dilution thereof, was compared to activity in a control devoid of inhibitor and the result reported below as that of inhibitor concentration effecting 50% inhibition of the stromelysin activity (IC_{50}).

In the following results the potencies of the compounds of examples 1-10 above in the above tests are compared in the same tests with the products of examples 13 and 27 of EP-A-236872 (Roche), namely:

[4-(N-hydroxyamino) 2(R)-isobutylsuccinyl)]-L-leucyl-L-alanine ethyl ester, and
[4-(N-hydroxyamino) 3(S)-phthaloylaminobutyl-2(R)-isobutylsuccinyl)]-L-leucyl

glycyl ethyl ester.

The former compound (hereafter referred to as C1) was chosen for comparison because of the collagenase inhibitors whose activity is reported in EP-A-236872, it is the most active. The latter compound (hereafter referred to as C2) was chosen for comparison because of the collagenase inhibitors whose activity is reported in EP-A-236872, it is the only one with a substituent in the position equivalent to the hydroxy substituent of the compounds of this invention.

Results:

Compound	Collagenase IC50	Stromelysin IC50
Example 1	5	60
Example 2	30	200
Example 3	100	not done
Example 4	10	not done
Example 5	20	not done
Example 6	30	3000
Example 7	150	500
Example 8	10	100
Example 9	30	not done
Example 10	8	200
C1	15	300
C2	7	70

Biological Example B

The concentration over time of compounds of the invention in the blood of laboratory animals following administration of the test compounds was measured.

Test compounds were administered by gavage to 6 male rats (300g) per treatment group. Blood samples were removed by tail venepuncture at 0.5, 1.0, 2.0, 6.0 and 24 hours post administration. 0.4 ml of blood was placed into 4.5ml tubes containing 0.1ml acid citrate dextrose (ACD) as anti-coagulant. For extraction, 3ml

methanol was added and the precipitated blood pelletted by centrifugation (30 min at 3000 rpm). A 2ml aliquot of supernatant was removed and concentrated by lyophilisation. The extract was redissolved in 200µl DMSO and a 10µl aliquot assayed for collagenase inhibitory activity. The inhibitory activity in the extracts was determined using the collagenase assay described in Biological Example A above, and the concentration of inhibitor (that is drug plus any active metabolites) obtained by comparison with standard curves. Results are expressed as peak concentration in ng/ml, as area under the curve (AUC) in ng/ml x hours, over 0-6 hours, and as AUC in number of IC_{50}'s x hours.

The compound of examples 1 and 10 above were compared with the comparison compounds C1 and C2.

Results

Compound	Peak conc ng/ml	AUC (0-6h) ng/ml x h	AUC (0-6h) n IC_{50}'s x h
Example 1*	59 @ 0.5h	143.25	46.2
Example 10	139 @ 0.5h	343	190
C1	25 @ 0.5h	91.7	7.4
C2	1@ 1h	5.3	2.12

* average of two results

Biological Example C

The activities of the compound of example 1 above and comparison compound C1 (see Biological Example A above) were assessed in an adjuvant-induced arthritis model.

Adjuvant arthritis was produced in male Lewis rats (Charles River) by a single intradermal injection of 0.75 mg of <u>M. butyricum</u> in light paraffin oil (Freunds complete adjuvant - FCA) into the base of the tail. The "secondary" lesion occurs after a delay of 10 days, and is characterised by inflammation of the hindpaws. Hindpaw edemia volumes were measured plethysmographically by water

displacement. The test compound was dosed b.i.d. from days 13 to 17. Paw volume on day 20 was measured and compared to that on day 13. The experiment was terminated on day 23.

On day 20, the compound of example 1 (dosed at 10 mg/kg) showed a statistically significant ($p<0.01$) reduction in swelling relative to control, whereas compound C1 had no effect.

Biological Example D

The compound of example 1 above was tested for activity *in vivo* in a rat mammary carcinoma model. A lung colonisation assay was performed in order to determine whether the compound of example 1 above is effective in inhibiting lung colonisation by circulating HOSP1.P mammary carcinoma cells after oral administration.

HOSP1.P cells (1×10^5 cells/animal) were administered to two groups of 12 rats by injection into the jugular vein. The product of example 1 was administered p.o. to one group at 30mg/kg at -4, +1, +6, +24 and +72 hours relative to tumour cell inoculation at 0 hours. The second (control) group received only vehicle (p.o.) by the same schedule. Animals were killed after 34 days. Lungs were removed and individual tumopurs counted after 24 hours fixation in Methacarn. No extrapulmonary tumours were found. Treatment with the product of example 1 resulted in a significant inhibition of lung colonisation relative to the control group. ($p<0.01$, Mann-Whitney, two tailed).

Results:

Lung Colony Number:

Group	Mean	Standard Deviation	Median	p
Control	70.50	27.74	71.50	-
Treated	38.91	12.49	38.50	<0.01

Biological Example E

The ability of compounds of the invention to inhibit the release of TNF was investigated. The assay is based on the ability of phorbol myristate acetate (PMA) to stimulate the release of TNF α from a human monocytic cell line, U937.

U937 cells cultured in RPMI 1640 medium + 5% foetal calf serum are centifuged at 1000 x g for 5 minutes and then resuspended in medium at 2 x 10^6 / ml. 1 ml of cell suspension is aliquoted into individual wells of 24-well plates. Test compounds are dissolved in dimethyl sulphoxide (DMSO) at a stock concentration of 100mM, then diluted to 50x the final required concentration with RPMI 1640 medium. 20µl of the diluted compounds are added to U937 cells in duplicate wells. TNF α release is stimulated by addition of PMA to the cells at a final concentration of 50nM. Appropriate control cultures are set up in duplicate. The plates are incubated for 18 hours at 37°C, 5% CO_2, then centrifuged at 1000 x g for 5 minutes. A specific ELISA for TNF α obtained from British Bio-technology Products Limited, Abingdon, England is used to measure TNF α levels in the culture supernatants

The average concentration of test compound which inhibits the release of TNF α by 50% relative to the control culture was assessed. The compounds of examples 1,2, 5 and 10 above were tested and had IC_{50} values less than 50µM.

Aqueous Solubility Example

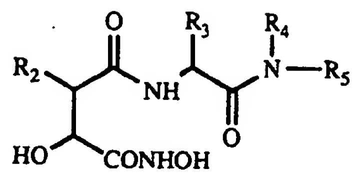
The solubilities of compounds of the invention in water at ambient temperature were measured, and compared with comparison compounds C1 and C2 (identified in Biological Example A above).

Results:

Compound	Solubility mg/ml
Example 1	0.1
Example 2	13.13
Example 3	2.34
Example 4	0.11
Example 5	0.14
Example 6	0.33
Example 7	0.18
Example 9	1.8
Example 10	1.4
C1	0.3
C2	<0.1

Claims:

1. A compound of formula (I) :



(I)

wherein

R_2 represents a group R_6-A- wherein A represents a divalent straight or branched, saturated or unsaturated hydrocarbon chain of up to 6 C atoms which may be interrupted by an O or S atom, and R_6 represents hydrogen or an optionally substituted phenyl, cycloalkyl or cycloalkenyl group;

R_3 represents a group R_7-$(B)_n$- wherein n is 0 or 1, B represents a divalent straight or branched, saturated or unsaturated hydrocarbon chain of up to 6 C atoms which may be interrupted by an O or S atom, and R_7 is -CONHOH, carboxyl, esterified or amidated carboxyl, cycloalkyl, cycloalkenyl, heterocyclyl, phenyl, napthyl, or substituted phenyl or napthyl in which the substituent(s) are selected from phenyl, hydroxy, C_1-C_6 alkoxy, benzyloxy, or R_8-(C=O)-(C_1-C_6alkyl)-O- wherein R_8 is hydroxy, amino, or an amino acid residue linked via an amide bond; or (except when n=0) R_7 is hydrogen;

R_4 represents hydrogen or methyl;

R_5 represents hydrogen, C_1-C_6 alkyl or a group D-(C_1-C_6 alkyl) wherein D represents hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, acylamino, optionally substituted phenyl, or a heterocyclic group, NH_2, or a mono- or di-(C_1-C_6 alkyl) amine or a heterocyclic group;

or R_3 and R_5 taken together represent a divalent, saturated or unsaturated hydrocarbon chain of from 8-14 C atoms, which may be interrupted by an O,

S or N heteroatom,

or a salt, solvate or hydrate thereof,

provided that R_3 is not the characteristic side chain of a natural alpha-amino acid, or the characteristic side chain of a natural alpha-amino acid in which any functional substituents are protected, any amino groups are acylated, and any carboxyl groups are esterified.

2. A compound as claimed in claim 1 wherein the stereochemistry is as follows:

C atom carrying the hydroxy group and hydroxamic acid moiety - S,
C atom carrying the R_2 group - R,
C atom carrying the R_3 group - S.

3. A compound as claimed in claim 1 or claim 2 wherein R_2 represents C_3-C_6 alkyl, cycloalkyl(C_3-C_6 alkyl), phenyl(C_2-C_6 alkyl), C_2-C_4 alkoxy(C_1-C_3 alkyl)$_m$, or C_2-C_4 alkylsulphanyl(C_1-C_3 alkyl)$_m$ group where m is 0 or 1.

4. A compound as claimed in claim 3 wherein R_2 represents n-pentyl, cyclohexylpropyl, cyclohexylbutyl, cyclohexylpentyl, phenylethyl, phenylpropyl, phenylbutyl, phenylpentyl, propyloxymethyl, or propylsulphanyl.

5. A compound as claimed in claim 3 wherein R_2 represents isobutyl.

6. A compound as claimed in any one of the preceding claims wherein R_3 represents a phenyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, phenyl(C_1-C_6 alkyl), substituted phenyl(C_1-C_6 alkyl), cycloalkyl, cycloalkyl(C_1-C_6 alkyl), thienyl, thienyl(C_1-C_6 alkyl), pyridyl(C_1-C_6 alkyl), thiazolyl(C_1-C_6 alkyl), thiofuranyl(C_1-C_6 alkyl), benzothiofuranyl(C_1-C_6 alkyl) or imidazolyl(C_1-C_6 alkyl) group, or R_3 and R_5 taken together may form a C_7-C_{12} alkylene chain, optionally interrupted by an O, S or N heteroatom.

7. A compound as claimed in claim 6 wherein R_3 represents phenyl, t-butyl, cyclohexylpropyl, cyclohexylbutyl, cyclohexylpentyl, optionally substituted phenylethyl, phenylpropyl, phenylbutyl and phenylpentyl in which the optional substituent(s) are in the phenyl ring and are selected from phenyl, hydroxy, C_1-C_6 alkoxy, benzyloxy, tetrafluoromethyl, halo (eg chloro) and R_8-(C=O)-(C_1-C_6alkyl)-O- wherein R_8 is hydroxy, amino, or an amino acid residue linked via an amide bond

8. A compound as claimed in claim 6 wherein R_3 represents phenylethyl, cyclohexyl, thienyl(C1-C6 alkyl), pyridylmethyl, thiazolylmethyl, thiofuranylmethyl, benzothiofuranylmethyl or imidazolylmethyl, 1-ethenyl, 1-propenyl, 1-propynyl, 2,2-dimethylpropyl, napthyl, napthylmethyl, propyloxymethyl, butyloxymethyl, and propylsulphanylmethyl, or butylsulphanylmethyl.

9. A compound as claimed in claim 6 wherein R_3 represents cyclohexylmethyl, t-butyl, 2-thienylmethyl, (4-hydroxycarbonylmethoxy)phenylmethyl, (4-phenyl)phenylmethyl, methoxycarbonylethyl, or N-hydroxyaminocarbonylethyl.

10. A compound as claimed in any one of the preceding claims wherein R_4 represents methyl or ethyl.

11. A compound as claimed in any one of claims 1 to 9 in which R_4 is hydrogen.

12. A compound as claimed in any one of the preceding claims wherein R_5 represents hydrogen or C_1-C_4 alkyl, or a group D-(C_1-C_6 alkyl) wherein D represents hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, acylamino, optionally substituted phenyl, or a heterocyclic group.

13. A compound as claimed in claim 12 wherein R_5 represents propyl, butyl, hydroxyethyl, 2-ethylthioethyl, 2-acetoxyethyl, N-acetyl-2-aminoethyl, 3-(2-pyrrolidone)propyl, optionally substituted phenylethyl, phenylpropyl, phenylbutyl or phenylpentyl.

14. A compound as claimed in claim 12 wherein R_5 is methyl or ethyl.

15. A compound selected from the group consisting of;

N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy) phenylalanine-N^1-methylamide;
N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-phenylglycine-N^1-methylamide;
N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-(4-phenyl)-phenylalanine-N^1-methylamide;
N^3-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]amino-1-azacyclotridecan-2-one;
N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-(1-pyrazolyl) alanine-N^1- methylamide;
N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-4-(N-hydroxyamino)glutamic acid-N^1-methylamide;
N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-(2-thienyl) alanine-N^1- methylamide;
N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-cyclohexyl alanine-N^1-(3-(2-pyrrolidone)propyl)amide,

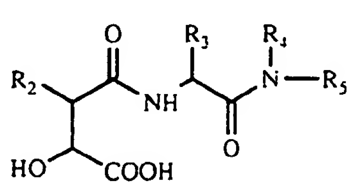
and salts, solvates or hydrates thereof.

16. N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-cyclohexyl alanine-N^1 methylamide, or a salt, solvate or hydrate thereof.

17. N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-tert-leucine-N^1-methylamide, or a salt, solvate or hydrate thereof.

18. A process for the preparation of a compound as claimed in claim 1 comprising:

(a) coupling an acid of general formula (II)



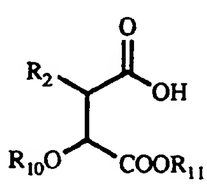
(II)

or an activated derivative thereof with hydroxylamine, O-protected hydroxylamine, or a salt thereof, R_2, R_3, R_4, and R_5 being as defined in general formula (I) except that any substituents in R_2, R_3, R_4, and R_5 which are potentially reactive with hydroxylamine, O-protected hydroxylamine or their salts may themselves be protected from such reaction, then removing any protecting groups from the resultant hydroxamic acid moiety and from any protected substituents in R_2, R_3, R_4, and R_5; and

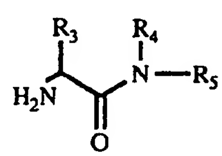
(b) optionally converting a compound of general formula (I) into another compound of general formula (I).

19. A process as claimed in claim 18 wherein an activated derivative of a compound of formula (II) is used and said activated derivative is a pentafluorophenyl, hydroxysuccinyl, or hydroxybenztriazyl ester.

20. A process as claimed in claim 18 or claim 19 wherein the compound of formula (II) is prepared by by coupling an acid of formula (III) or an activated derivative thereof with an amine of formula (IV)



(III)

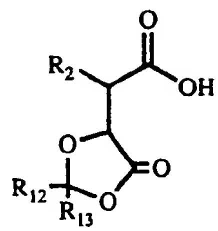


(IV)

wherein R_2, R_3, R_4, and R_5 are as defined in general formula (I) and R_{10} and R_{11} separately represent hydroxy protecting groups or taken together represent a divalent moeity which simultaneously protects both hydroxy groups, and subsequently removing the protecting groups or protecting moeity.

21. A process as claimed in claim 20 wherein an activated derivative of a compound of formula (III) is used and said activated derivative is a pentafluorophenyl ester, acid anhydride or acid halides, eg chloride.

22. A process as claimed in claim 20 or claim 21 wherein compound (III) has the formula (V):



(v)

wherein R_2, R_3, R_4, and R_5 are as defined in general formula (I) and the groups R_{12} and R_{13} are derived from a dioxalone forming reagent.

23. A process as claimed in claim 22 wherein the groups R_{12} and R_{13} are hydrogen, alkyl, phenyl or substituted phenyl.

24. A method of management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs and/or TNF in mammals including humans, which method comprises administering to the mammal an effective amount of a compound as claimed in any one of claims 1 to16.

25. A compound as claimed in any one of claims 1 to17 for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs and/or TNF.

26. A compound as claimed in any one of claims 1 to17 for use in human or veterinary medicine in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs and/or TNF.

27. The use of a compound as claimed in any one of claims 1 to17 in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs and/or TNF.

28. A method as claimed in claim 24, a compound for use as claimed in claim 25 or claim 26, or the use as claimed in claim 27, wherein the diseases or condition referred to is one mediated by an MMP.

29. A method as claimed in claim 24, a compound for use as claimed in claim 25 or claim 26, or the use as claimed in claim 27, wherein the diseases or condition referred to is rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration or tumour invasion by secondary metastases.

30. A method as claimed in claim 24, a compound for use as claimed in claim 25 or claim 26, or the use as claimed in claim 27, wherein the diseases or condition referred to is one mediated by TNF.

31. A method as claimed in claim 24, a compound for use as claimed in claim 25 or claim 26, or the use as claimed in claim 27, wherein the disease or condition referred to is inflammation, fever, cardiovascular effects, haemorrhage, coagulation and acute phase response, cachexia and anorexia, an acute infection, a shock state, a graft versus host reaction or autoimmune disease.

32. A pharmaceutical or veterinary composition comprising a compound as claimed in any one of claims 1 to 17 together with a pharmaceutically or veterinarily acceptable excipient or carrier.

33. A pharmaceutical or veterinary composition as claimed in claim 32 which is adapted for oral administration.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/01557

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07C259/06; A61K31/16; A61K31/19; C07D225/02
C07D231/12; C07D333/24; C07D207/27

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07C ; A61K ; C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 236 872 (F. HOFFMANN-LA ROCHE AG) 16 September 1987 cited in the application see claims; examples	1-33
A	WO,A,9 102 716 (BRITISH BIO-TECHNOLOGY LIMITED) 7 March 1991 see claims; examples	1-33

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18 OCTOBER 1993	15. 11. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SANCHEZ Y GARCIA J.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 18/10/93
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82